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# Ibrutinib, lenalidomide, and rituximab in relapsed or refractory mantle cell lymphoma (PHILEMON): a multicentre, open-label, single-arm, phase 2 trial

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## Summary

**Background** Regimens based on ibrutinib alone and lenalidomide and rituximab in combination show high activity in patients with relapsed or refractory mantle cell lymphoma. We hypothesised that the combination of all three drugs would improve efficacy compared with previously published data on either regimen alone.

**Methods** In this multicentre, open-label, single-arm, phase 2 trial, we enrolled patients aged 18 years or older with relapsed or refractory mantle cell lymphoma who had previously been treated with at least one rituximab-containing regimen, an Eastern Cooperative Oncology Group performance status score of 0–3, and at least one site of measurable disease, and who met criteria for several laboratory-assessed parameters. Treatment was divided into an induction phase of 12 cycles of 28 days with all three drugs and a maintenance phase with ibrutinib and rituximab only (cycle duration 56 days), given until disease progression or unacceptable toxicity. In the induction phase, patients received intravenous (375 mg/m<sup>2</sup>) or subcutaneous (1400 mg) rituximab once a week during cycle 1 and then once every 8 weeks. Oral ibrutinib (560 mg once a day) was given to patients every day in the cycle, whereas oral lenalidomide (15 mg once a day) was given on days 1–21. The primary endpoint was overall response assessed in the intention-to-treat population according to Lugano criteria. Safety analysis included all patients who received the treatment, irrespective of eligibility or duration of treatment. The trial is ongoing, but is no longer accruing patients, and is registered with ClinicalTrials.gov, number NCT02460276.

**Findings** Between April 30, 2015, and June 1, 2016, we enrolled 50 patients with relapsed or refractory mantle cell lymphoma at ten centres in Sweden, Finland, Norway, and Denmark. At a median follow-up of 17·8 months (IQR 14·7–20·9), 38 (76%, 95% CI 63–86) patients had an overall response, including 28 (56%, 42–69) patients who had a complete response and ten (20%, 11–33) who had a partial response. The most common grade 3–4 adverse events were neutropenia (in 19 [38%] of 50 patients), infections (in 11 [22%] patients), and cutaneous toxicity (in seven [14%] patients). There were three treatment-related deaths during the study, two due to sepsis and one due to embolic stroke.

**Interpretation** Our results provide preliminary evidence that the triplet combination of ibrutinib, lenalidomide, and rituximab is an active regimen in patients with relapsed or refractory mantle cell lymphoma, and should be evaluated in a prospective randomised controlled trial.

**Funding** Janssen and Celgene.

## Introduction

Relapsed or refractory mantle cell lymphoma is associated with poor outcomes. The choice of therapy depends on the efficacy of previous lines of treatment.<sup>1</sup> In many cases of disease progression, a non-cross-resistant chemotherapy regimen is the next choice, usually in combination with the anti-CD20 antibody rituximab. In patients with chemorefractory disease or early relapse, non-chemotherapeutic alternatives might be considered. Among such drugs active in relapsed or refractory mantle cell lymphoma are bortezomib, temsirolimus, lenalidomide, ibrutinib, and venetoclax.<sup>2–6</sup> Lenalidomide is an immunomodulatory drug with antiangiogenic and antineoplastic properties. In B-cell malignancies, lenalidomide interacts with the ubiquitin E3 ligase cereblon and enhances its enzymatic activity to degrade the

transcription factors IKZF1 (DNA-binding protein Ikaros) and IKZF3 (zinc finger protein Aiolos), leading to reduced activity of IRF4 (interferon regulatory factor 4), a downstream target of cereblon. This downregulation of IRF4 leads to proliferation and activation of natural killer cells, thereby enhancing natural killer cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity.<sup>7</sup> In this respect, lenalidomide acts as an immunosensitiser, enhancing the activity of rituximab. The combination of rituximab and lenalidomide has been shown to be very active in mantle cell lymphoma, in both relapsed and front-line settings.<sup>8,9</sup>

The introduction of ibrutinib, an inhibitor of Bruton's tyrosine kinase, was considered a major step forward in the treatment of mantle cell lymphoma. Its activity is substantially higher than other single drugs used in the

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## Research in context

### Evidence before this study

We searched PubMed without language restrictions for clinical trials published up to Dec 5, 2013, using the search term "ibrutinib, rituximab, and lenalidomide". We also searched the EU Clinical Trials Register and ClinicalTrials.gov using the same search term. We found no trials examining the combination of these drugs in the treatment of mantle cell lymphoma. At the annual meeting of the American Society of Hematology in December, 2015, Ujjani and colleagues presented the results of a phase 1 trial of lenalidomide, rituximab, and ibrutinib in previously untreated patients with follicular lymphoma. They found no clear benefit for the triplet regimen over the combination of rituximab and lenalidomide in terms of efficacy, but a high incidence of grade 3 cutaneous toxicity (36%).

### Added value of this study

To the best of our knowledge, this study is the first to assess the non-chemotherapeutic combination of lenalidomide, rituximab, and ibrutinib in patients with relapsed or refractory mantle cell lymphoma. Compared with previous studies of ibrutinib alone or in combination with rituximab, the triplet regimen was associated with increased haematological toxicity and infections,

but also appeared to be more active in terms of complete responses. The effect of specific mutations and copy-number alterations has not previously been investigated in a prospective clinical trial of a non-chemotherapy regimen for mantle cell lymphoma. We showed that the combination of lenalidomide, rituximab, and ibrutinib might overcome the adverse prognostic effects of *TP53* mutations and *CDKN2A-TP53* deletions. Additionally, evaluation of minimal residual disease in bone marrow and peripheral blood with real-time PCR has not previously been reported in a trial of a non-chemotherapeutic regimen for mantle cell lymphoma. We found that a molecular remission could be obtained in a high proportion of patients, including in those with *TP53* mutation.

### Implications of all the available evidence

Our findings indicate that the combination of lenalidomide, rituximab, and ibrutinib might be an active regimen in patients with relapsed or refractory mantle cell lymphoma, particularly in the subset of patients with high-risk genetic features, such as *TP53* mutations or combined deletions of *TP53* and *CDKN2A*. For this subset of patients, the triplet regimen might be used as a bridge to allogeneic stem-cell transplantation.

treatment of this cancer, with 65–70% of patients having a confirmed response in both phase 2 and phase 3 trials.<sup>5,10</sup> Because ibrutinib also modulates the microenvironment in vivo, synergy with the immunosensitising effects of lenalidomide could be expected.<sup>11</sup> Ibrutinib in combination with lenalidomide might also counteract possible antagonism between ibrutinib and rituximab.<sup>12,13</sup>

Based on the high activity and good tolerability of both ibrutinib alone and rituximab and lenalidomide in combination, we aimed to assess the efficacy and safety of the triplet combination in patients with relapsed or refractory mantle cell lymphoma. Moreover, we aimed to investigate the proportion of patients who achieved molecular remission with this regimen and its activity with regard to specific mutations commonly present in mantle cell lymphoma, such as *TP53* mutations, which are associated with poor outcomes in the front-line setting.<sup>14</sup>

## Methods

### Study design and participants

We did an open-label, single-arm, multicentre, phase 2 trial at ten centres in Sweden, Finland, Norway, and Denmark (appendix p 8). Eligible patients were older than 18 years; had previously been treated with at least one rituximab-containing regimen, with no upper limit on the number of previous treatments received; and had histologically confirmed mantle cell lymphoma, an Eastern Cooperative Oncology Group performance status score of 0–3, at least one site of measurable disease (>1.5 cm long axis), an absolute neutrophil count of 1000 cells per  $\mu\text{L}$  or higher, a platelet count of

100 000 per  $\mu\text{L}$  or higher (or  $\geq 50\,000$  per  $\mu\text{L}$  in cases of bone marrow involvement), alanine aminotransferase and aspartate aminotransferase levels three times lower than the upper limit of normal, and serum creatinine concentrations no greater than two times the upper limit of normal. A washout period of 3 weeks since previous therapy was required. Key exclusion criteria included known CNS involvement, HIV infection, active hepatitis B or C virus infection, stroke or intracranial haemorrhage (within 6 months before enrolment), need for anticoagulation with warfarin (or equivalent vitamin K antagonist), or treatment with strong or moderate CYP3A (cytochrome P450 3A4) inhibitors. Previous treatment with ibrutinib or lenalidomide was allowed.

The study was approved by the national ethics committee in each country and done according to the Declaration of Helsinki and International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent.

### Procedures

At the time of initiation of this study, a phase 1 trial<sup>15</sup> of the combination of ibrutinib, rituximab, and lenalidomide in patients with follicular lymphoma was ongoing. We selected doses of lenalidomide and ibrutinib on the basis of this previous trial.<sup>15</sup> Treatment was divided into an induction phase of 12 cycles of 28 days with all three drugs and a maintenance phase with ibrutinib and rituximab only (cycle duration 56 days), given until disease progression or unacceptable toxicity. Patients received rituximab once a week for 4 weeks during cycle 1, then every 8 weeks. The initial dose of rituximab

See Online for appendix

was given intravenously at 375 mg/m<sup>2</sup>; subsequent doses could then either be given intravenously at the same dose or as a subcutaneous injection of 1400 mg to remove the need for intravenous access. No dose reductions were permitted for rituximab. Ibrutinib was given orally (560 mg once a day) on days 1–28, and lenalidomide was given orally (15 mg once a day) on days 1–21. Doses of lenalidomide and ibrutinib were reduced in cases of grade 3 or 4 neutropenia and thrombocytopenia. In such cases, ibrutinib was reduced from 560 mg per day to 420 mg per day and then to 280 mg per day; lenalidomide was reduced from 15 mg per day to 10 mg per day and then to 5 mg per day.

Study treatment was terminated in cases of progressive disease or grade 4 non-haematological toxicity, if requested by a patient, or if the treating physician thought a change of therapy would be in the best interest of the patient.

To assess minimal residual disease at baseline, DNA was extracted from lymphoma cells in bone marrow with the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany) and used for design of primers for PCR amplification of patient-specific clonally rearranged immunoglobulin heavy chain genes (*IGH*) and detection of the *CCND1-IGH* translocation t(11;14). PCR was done with the TaqMan Gene Expression Master Mix (Thermo Fisher Scientific, Waltham, MA, USA). The sensitivity of the assay for minimal residual disease was one in 10<sup>5</sup> cells, except for four patients in whom the sensitivity of the assay was one in 10<sup>4</sup> cells. For patients with less than 1% tumour cells in bone marrow at baseline, a quantitative assay for minimal residual disease was not feasible and, instead, a qualitative nested PCR assay was done, as previously described.<sup>16</sup>

For genetic analyses, we did next-generation sequencing using Ion Torrent technology (ThermoFisher Scientific, Waltham, MA, USA) to analyse DNA from bone marrow specimens taken at baseline for mutations in selected coding regions, splice sites, and untranslated regions of *ATM*, *KMT2D*, *CCND1*, *TP53*, *WHSC1*, *BIRC3*, *NOTCH1*, and *NOTCH2*, as described previously.<sup>14</sup> The cutoff for calling a variant was 5% in general and 3% for *TP53* mutations. Median coverage for all runs was 2575×, and the limit for calling a variant was 400×. Chromosome 17p13 (*TP53*) and chromosome 9p21 (*CDKN2A*) deletions were identified by droplet digital PCR with the QX200 system (Bio-Rad Laboratories, Hercules, CA, USA), as described previously.<sup>14</sup> Copy number loss was defined as copy number less than 1.95. Each sample was analysed at least twice and deletions were called with QuantaSoft software version 1.7 (Bio-Rad Laboratories, Hercules, CA, USA). The people who did the genetic analyses were masked to patient characteristics and outcomes.

## Outcomes

The primary endpoint was overall response assessed according to Lugano criteria,<sup>17</sup> with restaging every 12 weeks during the induction phase according to results

of CT and bone marrow examination. PET scans were done to confirm complete responses or at the time of maximal tumour regression. During the maintenance phase, CT and bone marrow examination were done every 6 months. Evaluation of CT and PET scans was done at the individual study centres.

Secondary endpoints included proportion of patients who achieved a complete response (assessed with and without PET), response duration (time from date of response to date of disease progression or death), proportion of patients who achieved molecular remission, molecular remission duration (time from date of molecular remission to date of molecular relapse or death), progression-free survival (time from enrolment to date of disease progression, death from any cause, or last available follow-up), and overall survival (time from enrolment to date of death or last available follow-up). In a post-hoc analysis, factors predictive of progression-free and overall survival were evaluated. Safety was also a secondary endpoint, assessed with adverse event monitoring and laboratory analyses. Adverse events were assessed according to the Common Toxicity Criteria for Adverse Events, version 4.03. We also investigated the presence of biomarkers, including specific mutations and chromosomal deletions. Health-related quality of life was assessed with the European Organisation for Research and Treatment of Cancer QLQ-C30 questionnaire, although the results of this analysis will be reported elsewhere. Minimal residual disease in blood and bone marrow specimens after cycles 6, 12, 18, and 24 using real-time PCR, according to EuroMRD criteria, was also assessed as a secondary endpoint.<sup>18</sup> Genetic analyses were exploratory.

## Statistical analysis

According to Fleming's single-stage procedure (type I error  $\alpha$  of 0.05 and power of 0.8), to achieve an overall response in more than 85% of patients (chosen to be superior to the 75 [68%] of 111 patients who had an overall response in a previous phase 2 trial<sup>5</sup> of ibrutinib alone;  $p < 0.05$ ), 40 patients would need to be recruited. If 34 or more patients had a response, the null hypothesis could be rejected. The primary analysis was done by intention to treat. The safety analysis included all patients who received the treatment, irrespective of eligibility or duration of treatment. To account for loss of 20% of patients because of ineligibility and early progression, a total sample size of 50 patients was required.

Descriptive statistics were used to summarise patient demographics and baseline characteristics. We used the Kaplan-Meier method to estimate progression-free survival and overall survival. Univariate and multivariate analyses were done with the Cox proportional-hazards regression model. All statistical analyses were done with IBM SPSS version 22.0.

This trial is registered with ClinicalTrials.gov, number NCT02460276.

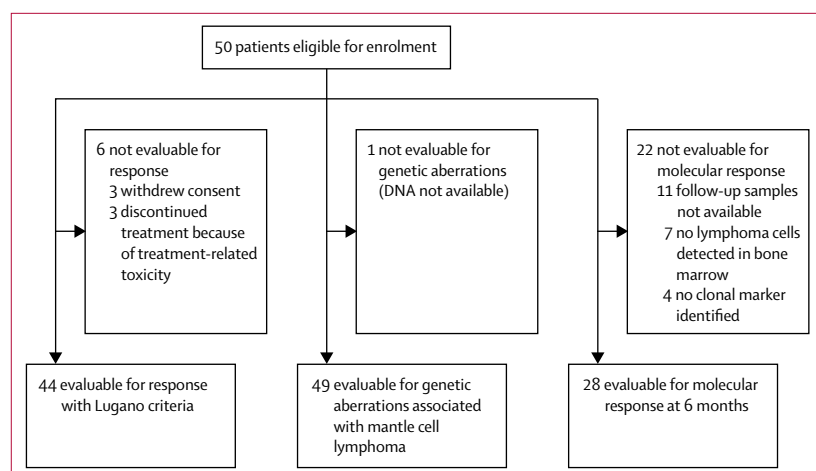


Figure 1: Patient flow diagram

All patients (n=50)	
Age (years)	69 (45–85)
Sex	
Female	14 (28%)
Male	36 (72%)
ECOG performance status score 0–1	45 (90%)
MIPI score	
Low risk (<5.7)	8 (16%)
Intermediate risk (5.7–6.1)	15 (30%)
High risk (>6.2)	23 (46%)
Missing	4 (8%)
Ann Arbor stage IV disease	42 (84%)
Bone marrow involvement	34 (68%)
Refractory disease	8 (16%)
Number of previous therapies	2 (1–7)
Previous therapy	
Autologous stem-cell transplantation	21 (42%)
Allogeneic stem-cell transplantation	3 (6%)
Ibrutinib	4 (8%)
Lenalidomide	1 (2%)
Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group. MIPI=Mantle Cell Lymphoma International Prognostic Index.	
<b>Table 1: Patient and disease characteristics</b>	

### Role of the funding source

The funders were not involved in the protocol writing, data collection, data analysis, data interpretation, or writing of the report, but did review the manuscript before submission. All authors had full access to the raw data and approved the final submitted version. The corresponding author had the final decision to submit for publication.

### Results

Between April 30, 2015, and June 1, 2016, we enrolled 50 patients with relapsed or refractory mantle cell lymphoma from ten centres in Sweden, Finland, Norway,

and Denmark (figure 1). Table 1 shows the patients' characteristics at baseline. 44 (88%) of 50 patients were evaluable for response with Lugano criteria. Six patients were not evaluable because of withdrawn consent (n=3) or discontinuation of treatment because of treatment-related toxic effects, including sepsis (n=2) and fatigue (n=1), before response evaluation.

At a median follow-up of 17.8 months (IQR 14.7–20.9), 38 (76%, 95% CI 63–86) of 50 patients had an overall response (table 2). 28 (56%, 42–69) patients had a complete response and ten (20%, 11–33) had a partial response (table 2). Of the 27 patients in whom PET was done for response evaluation, 21 (78%) had a complete response, five (19%) had a partial response, and one (4%) had stable disease.

Median progression-free survival was 16.0 months (95% CI 13.7–20.5) and median overall survival was 22.0 months (19.5–23.8; figure 2); 12-month progression-free survival was 56.9% (95% CI 42.7–71.1) and 12-month overall survival was 77.6% (65.6–89.6). Overall median duration of response was not reached (95% CI not calculable). The 28 patients who achieved a complete response had a longer median duration of response (not reached [95% CI not calculable]) than the ten patients who achieved a partial response (8.9 months [95% CI 6.3–13.8]). Four patients who had disease progression on ibrutinib were included, of whom one achieved a partial response (which is still ongoing after 13 months), one had stable disease, and two progressed early on study treatment. None of the eight patients with a low-risk score in the Mantle Cell Lymphoma International Prognostic Index (MIPI) progressed during the study. In an exploratory post-hoc analysis, MIPI score was the only factor predictive of outcome, in terms of progression-free survival (appendix p 9).

49 (98%) of 50 patients were evaluable for genetic aberrations associated with mantle cell lymphoma. We found no difference in overall response between patients with and without *TP53* mutations (eight [73%, 95% CI 39–94] of 11 patients with mutations, including seven [64%, 31–89] with a complete response, vs 30 [79%, 63–90] of 38 patients without mutations, including 21 [55%, 38–71] with a complete response; table 2). Although patients with *TP53* mutations appear to have longer progression-free survival, there was no difference in progression-free survival according to the univariate analysis (hazard ratio [HR] 2.0, 95% CI 0.85–4.8, p=0.11; appendix pp 1, 9), even after adjusting for MIPI score, sex, and deletion of *CDKN2A* and *TP53* in the multivariate analysis (2.6, 0.57–11.0, p=0.22; appendix p 9). 14 patients presented with deletion of both *CDKN2A* and *TP53*, 12 (86%) of whom responded to treatment. The presence of a deletion in both *CDKN2A* and *TP53* had no effect on progression-free or overall survival (appendix pp 2, 9). Similarly, we found no association between any other specific genetic abnormality and outcome (data not shown).



Of 49 patients with available DNA, 22 (45%) harboured at least one mutation in genes commonly mutated in mantle cell lymphoma (figure 3). The most common mutations were found in *TP53* (in 11 [22%] patients), *ATM* (in eight [16%] patients), and *KMT2D* (in seven [14%] patients). Detailed information about the detected mutations can be found in the appendix (pp 6,7).

*CDKN2A* deletions were detected in 28 (58%) of 48 evaluable patients and *TP53* deletions in 17 (35%) of 49 evaluable patients (figure 3). 14 (29%) of 48 patients presented with both deletions.

After 6 months, 28 (56%) of 50 patients were evaluable for minimal residual disease. 22 patients were not evaluable because follow-up samples were not available because of early progression or withdrawal (n=11), no lymphoma cells were detectable in bone marrow (n=7), or no clonal marker could be identified (n=4; figure 1). Primers for *IGH* rearrangements were used in all cases, and in seven patients with the t(11;14) translocation, primers to the *CCND1-IGH* rearrangement were used. Eight patients with less than 1% tumour cells in bone marrow at baseline were assessed for molecular remission with qualitative nested PCR. At 6 months, 15 (56%) of 27 patients had molecular remission in peripheral blood and 12 (43%) had molecular remission in bone marrow. 13 (68%) of 19 patients had molecular remission in bone marrow at 12 months (table 3). The median duration of molecular remission was 3 months (IQR 3–9).

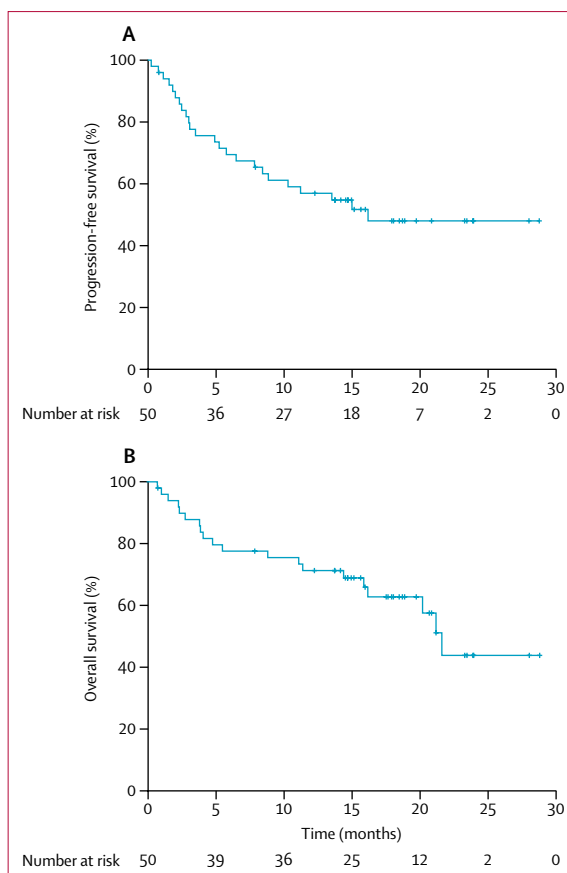
Patients who were negative for minimal residual disease in peripheral blood at 6 months had longer progression-free survival (median not reached [95% CI not calculable]) than patients who were positive for minimal residual disease in peripheral blood at 6 months (10·3 months [95% CI 5·6–15·0]; HR 0·14, 95% CI 0·03–0·71;  $p=0·017$ ; appendix p 3). The estimated 24-month progression-free survival for patients with molecular remission at 6 months was 82% (95% CI 69–96) compared with 42% (13–70) for patients not achieving molecular remission at 6 months. Furthermore, molecular remission in peripheral blood at 6 months was associated with longer overall survival (median not reached [95% CI not calculable] vs 20·0 months [9·8–31·0] for people who had not achieved molecular remission in peripheral blood at 6 months; HR 0·17, 95% CI 0·03–0·95;  $p=0·043$ ); the estimated 24-month overall survival for these patients was 67% (95% CI 36–97), compared with 44% (16–72) for patients positive for minimal residual disease at 6 months (appendix p 4). Among four patients with *TP53* mutation who were evaluable at 12 months, two were negative for minimal residual disease in bone marrow. All patients in molecular remission were in complete remission, based on Lugano criteria.

At a median follow-up of 17·8 months (IQR 14·7–20·9), treatment was discontinued in 34 (68%) of 50 patients because of progressive disease (in 17 [34%] patients),

	All patients (n=50)	<i>TP53</i> unmutated (n=38)	<i>TP53</i> mutated (n=11)
Overall response	38 (76%, 63–86)	30 (79%, 64–89)	8 (73%, 43–90)
Complete remission	28 (56%, 42–69)	21 (55%, 40–70)	7 (64%, 35–85)
Partial remission	10 (20%, 11–33)	9 (24%, 13–39)	1 (9%, 2–38)
Stable disease	1 (2%, 0–1)	1 (3%, 0–14)	0 (0%, 0–0)
Progressive disease	5 (10%, 4–21)	3 (8%, 3–21)	2 (18%, 5–48)
Not evaluable*	6 (12%, 6–24)	4 (11%, 4–24)	1 (9%, 2–38)

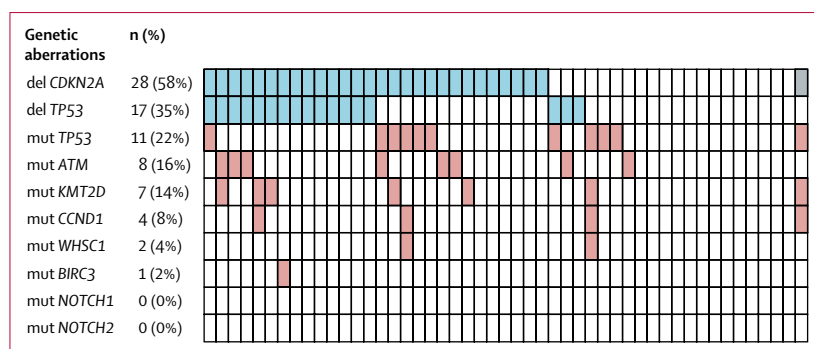
Data are n (%; 95% CI). \*Six patients were not evaluable because of withdrawal of consent (n=3) or treatment discontinuation because of treatment-related toxicity before response evaluation (n=3). One patient was not evaluable for *TP53* mutation status for technical reasons.

**Table 2: Maximal responses to treatment in all patients and according to presence of *TP53* mutation**



**Figure 2: Progression-free survival (A) and overall survival (B)**

allogeneic stem-cell transplantation (in three [6%] patients), other treatment-related toxic effects (five [10%]), withdrawal of consent (three [6%]), death related to treatment (three [6%]), and for unspecified reasons (three [6%]). Adverse events led to dose reduction of lenalidomide in



**Figure 3: Genetic aberrations detected in lymphoma cells in bone marrow at the time of relapse**  
Each column represents one patient (n=49). Blue squares indicate the presence of a deletion and red squares indicate the presence of a point mutation. The grey square indicates missing data for the CDKN2A deletion in one patient.

	6 months		12 months		18 months		24 months	
	Bone marrow (n=28)	Peripheral blood (n=27)	Bone marrow (n=19)	Peripheral blood (n=19)	Bone marrow (n=11)	Peripheral blood (n=12)	Bone marrow (n=5)	Peripheral blood (n=5)
Negative	12	15	13	11	3	6	3	4
Positive	16	12	6	8	8	6	2	1
Molecular remission (%)	43%	56%	68%	58%	27%	50%	60%	80%

**Table 3: Molecular remission in peripheral blood and bone marrow at 6, 12, 18, and 24 months**

	Grade 1–2*	Grade 3	Grade 4	Grade 5
<b>Haematological adverse events</b>				
Thrombocytopenia	8 (16%)	4 (8%)	2 (4%)	0 (0%)
Anaemia	8 (16%)	1 (2%)	0 (0%)	0 (0%)
Neutropenia	NR	13 (26%)	6 (12%)	0 (0%)
<b>Non-haematological adverse events</b>				
Gastrointestinal	34 (68%)	5 (10%)	1 (2%)	0 (0%)
Infections	18 (36%)	9 (18%)	2 (4%)	2 (4%)
Cutaneous	28 (56%)	7 (14%)	0 (0%)	0 (0%)
Fatigue	28 (56%)	1 (2%)	0 (0%)	0 (0%)
Muscle cramps	15 (30%)	3 (6%)	0 (0%)	0 (0%)
Respiratory	19 (38%)	1 (2%)	1 (2%)	0 (0%)
Neurological	19 (38%)	1 (2%)	0 (0%)	1 (2%)
Ocular	13 (26%)	0 (0%)	0 (0%)	0 (0%)
Psychiatric	6 (12%)	0 (0%)	0 (0%)	0 (0%)
Vascular	11 (22%)	5 (10%)	0 (0%)	0 (0%)
Renal	7 (14%)	0 (0%)	0 (0%)	0 (0%)
Atrial fibrillation	NR	1 (2%)	0 (0%)	0 (0%)

Data are n (%). The denominator is 50. NR=not reported. \*For grade 1–2 events, only those occurring in ≥10% of patients are reported.

**Table 4: Treatment-emergent adverse events**

five (10%) of 50 patients and of ibrutinib in two (4%) patients.

The most common grade 1–2 non-haematological adverse events are reported in table 4. Gastrointestinal toxicity generally occurred in the early phase of

treatment, with a median duration of 2 months (IQR 1–3). One patient developed an intracerebral haematoma after 12 months of treatment, leading to termination of ibrutinib; the patient recovered without residual symptoms and is still on maintenance treatment with rituximab. Atrial fibrillation was reported in four (8%) of 50 patients (one was grade 3). The most common grade 3–4 non-haematological adverse events (occurring in >10% of patients) were gastrointestinal toxicity (in six [12%] of 50 patients), infections (in 11 [22%] patients), and cutaneous toxicity (in seven [14%] patients; all grade 3). One patient developed Guillain-Barré syndrome, requiring ventilator support for 3.5 months. Grade 3–4 haematological adverse events included neutropenia in 19 (38%) patients, thrombocytopenia in six (12%) patients, and anaemia in one (2%) patient.

20 (40%) of 50 patients died during the study. The cause of death was disease progression in 17 (85%) of 20 patients and treatment related in three (15%) patients (two [10%] because of sepsis and one [5%] because of embolic stroke). The patient with embolic stroke also had atrial fibrillation and had received apixaban as thromboembolism prophylaxis, although apixaban had been stopped because of planned prostatic surgery.

## Discussion

In this study, we showed that the triplet regimen of ibrutinib, rituximab, and lenalidomide was an active combination in patients with relapsed or refractory mantle cell lymphoma. 76% (95% CI 63–86) of patients had an overall response; however, the lower bound of the 95% CI did not exceed the 68% (58–76) overall response with ibrutinib alone in a previous study,<sup>5</sup> suggesting that the triplet regimen might not be superior to ibrutinib alone, although such cross-trial comparisons should be made with caution. In 2016, Wang and colleagues<sup>19</sup> presented data on the combination of ibrutinib and rituximab in a patient population that was similar to our population. The proportion of patients who achieved an overall response in that trial<sup>19</sup> was slightly higher than that in this study (88% vs 76%), although similar when we excluded the six patients who either withdrew informed consent or dropped out because of early toxicity in this study (88% vs 86%). The population in the study by Wang and colleagues<sup>19</sup> was different to our population in terms of the proportion of patients with a low-risk MIPI score (44% in the study by Wang and colleagues vs 16% in our trial) and the proportion of patients with refractory disease (70% in the study by Wang and colleagues vs 16% in our trial).

Addition of lenalidomide to ibrutinib and rituximab might increase the proportion of patients who have complete remission, which was 56% in this study. Previous studies<sup>8,10,19</sup> reported complete responses in 44% of patients on ibrutinib and rituximab, in 36% of patients on rituximab and lenalidomide, and in 19% of patients on ibrutinib alone. However, 12-month progression-free

survival in our study was lower than reported in a phase 2 trial<sup>19</sup> of ibrutinib and rituximab (ie, without lenalidomide; 57% vs 75%), and median progression-free survival was not reached in that trial. In the phase 3 RAY trial<sup>10</sup> with ibrutinib alone, the median progression-free survival was 14·6 months, which was not much shorter than the 16 months in this study. A possible interpretation of these findings is that the triplet regimen might be associated with a deeper initial response, but that this response does not translate into longer progression-free survival.

In this study, patients with low-risk MIPI scores had good outcomes, with no such patients progressing during the study period. In three patients, the regimen was used as a bridge to allogeneic stem-cell transplantation as a potentially curative strategy.

In-vitro and translational studies<sup>12,13</sup> have suggested that rituximab and ibrutinib have antagonistic effects. This antagonism is believed to be due to off-target inhibitory effects of ibrutinib on interleukin-2 inducible tyrosine kinase (tyrosine-protein kinase ITK/TSK), potentially leading to inhibition of natural killer cells, as well as due to indirect mechanisms. At the time of initiation of this trial, we hypothesised that this antagonism might be reversed by lenalidomide because it is an activator of natural killer cells. However, subsequent in-vitro studies<sup>20</sup> have not confirmed this hypothesis, and the optimal sequence of ibrutinib and rituximab remains unknown. The in-vivo effect of combining immune modulation by ibrutinib with lenalidomide and antibodies targeting CD20 should be further investigated.<sup>11,21,22</sup>

The triplet regimen was associated with greater haematological toxicity, particularly neutropenia, than reported for the ibrutinib and rituximab combination.<sup>19</sup> This increased haematological toxicity is probably the cause of the increased incidence of grade 3–4 infections (22%) in our study. Cutaneous adverse events were also more common with the triplet regimen than with the doublet regimen, although we should be cautious about making direct comparisons between unrelated clinical trials; grade 3 reactions occurred in 14% of patients on the triplet regimen compared with 6% of patients on ibrutinib and rituximab.<sup>19</sup> In a study<sup>15</sup> of the triplet regimen in patients with untreated follicular lymphoma, the incidence of grade 3 rash was higher than observed in this study (36% vs 14%), indicating that this event might be less frequent in patients who have received previous chemotherapy than in those previously untreated with chemotherapy.

In a previous study,<sup>14</sup> we identified *TP53* mutations in about 10% of patients with untreated mantle cell lymphoma, and showed that, even with intensive immunochemotherapy and autologous stem-cell transplantation, the response to treatment and eventual outcome were poor for patients with *TP53* mutations. Our interpretation of these findings is that *TP53*-mutated mantle cell lymphoma constitutes a phenotypically distinct and highly aggressive

form of the disease, similar to the aggressive phenotype seen in *TP53*-mutated chronic lymphocytic leukaemia. Patients with mutations in *TP53* should probably not receive standard immunochemotherapy with or without autologous stem-cell transplantation, but rather be included in experimental, front-line trials exploring novel targeted drugs. To our knowledge, this study is the first to show that non-chemotherapeutic approaches might be active in the subpopulation of patients with *TP53* mutations. We found that similar proportions of patients with and without *TP53* mutations had an overall response and complete response, indicating a similarly high activity in these patients. Additionally, when correcting for other prognostic factors, no difference in progression-free survival was seen between patients with and without *TP53* mutations.

In a series from the European MCL Network,<sup>23</sup> combined deletion of *CDKN2A* and *TP53* was associated with very poor outcomes in patients treated upfront with immunochemotherapy and autologous stem-cell transplantation. These results were confirmed in our previous study<sup>14</sup> in younger patients with mantle cell lymphoma from the Nordic MCL2 and MCL3 trials. Double deletions were detected in 8% of the European MCL cohort and in 7% of the Nordic cohort. In this study, the frequency of double deletions was notably higher than in the previous studies, at 29%, but did not have an effect on prognosis. These differences might be explained by the substantially different setting of relapsed or refractory disease; however, the non-chemotherapeutic approach might have overcome the poor effect of these aberrations.

To our knowledge, previous studies of ibrutinib alone or in combination with other drugs have not included results on minimal residual disease. Here, we show that molecular remission might be achieved in a high proportion of cases and that negativity for minimal residual disease might be associated with improvement in both progression-free and overall survival. As shown previously,<sup>24</sup> examination of minimal residual disease in bone marrow was more sensitive than examination in peripheral blood.

In conclusion, we showed that the combination of ibrutinib, lenalidomide, and rituximab was an active regimen in patients with relapsed or refractory mantle cell lymphoma, with high proportions of complete and molecular responses. However, our data did not support that the triplet regimen is superior to the combination of ibrutinib and rituximab or ibrutinib alone in these patients. Unlike chemotherapy-based regimens, this novel triplet combination seemed to overcome the negative prognostic effects of *TP53* mutations and *CDKN2A-TP53* deletions.

#### Contributors

MJ, MH, RR, KFW, HK, AL, CHG, and AK designed the trial and wrote the study protocol. CWE, CD, and KG did the sequencing and copy number analyses. LBP and CUN did the minimal residual disease assessment. HT was responsible for trial coordination and data management. All authors had access to the raw data, contributed to the writing of the manuscript, and approved the final version for submission.



## Declaration of interests

MJ reports grants and non-financial support from Janssen and Celgene, during the conduct of the study, and grants and non-financial support from AbbVie, grants, personal fees, and non-financial support from Gilead, and personal fees from Janssen, outside the submitted work. MH reports grants, personal fees, and non-financial support from Janssen, Celgene, Takeda, and Genentech, outside the submitted work. CUN reports grants from Novo Nordisk Foundation, grants and personal fees from AbbVie, and personal fees from Gilead and Janssen, outside the submitted work. CHG reports personal fees from Janssen, outside the submitted work. AK reports grants and personal fees from Nordic Nanovector and grants from Roche and Merck, outside the submitted work. All other authors declare no competing interests.

## References

- Dreyling M, Campo E, Hermine O, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28** (suppl 4): iv62–71.
- O'Connor OA, Wright J, Moskowitz C, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *J Clin Oncol* 2005; **23**: 676–84.
- Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol* 2009; **27**: 3822–29.
- Trneny M, Lamy T, Walewski J, et al. Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial. *Lancet Oncol* 2016; **17**: 319–31.
- Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013; **369**: 507–16.
- Davids MS, Roberts AW, Seymour JF, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol* 2017; **35**: 826–33.
- Gribben JG, Fowler N, Morschhauser F. Mechanisms of action of lenalidomide in B-cell non-Hodgkin lymphoma. *J Clin Oncol* 2015; **33**: 2803–11.
- Wang M, Fayad L, Wagner-Bartak N, et al. Lenalidomide in combination with rituximab for patients with relapsed or refractory mantle-cell lymphoma: a phase 1/2 clinical trial. *Lancet Oncol* 2012; **13**: 716–23.
- Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment for mantle-cell lymphoma. *N Engl J Med* 2015; **373**: 1835–44.
- Dreyling M, Jurczak W, Jerkeman M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2016; **387**: 770–78.
- Niemann CU, Herman SE, Maric I, et al. Disruption of in vivo chronic lymphocytic leukemia tumor-microenvironment interactions by ibrutinib—findings from an investigator-initiated phase II study. *Clin Cancer Res* 2016; **22**: 1572–82.
- Skarzynski M, Niemann CU, Lee YS, et al. Interactions between ibrutinib and anti-CD20 antibodies: competing effects on the outcome of combination therapy. *Clin Cancer Res* 2016; **22**: 86–95.
- Kohrt HE, Sagiv-Barfi I, Rafiq S, et al. Ibrutinib antagonizes rituximab-dependent NK cell-mediated cytotoxicity. *Blood* 2014; **123**: 1957–60.
- Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood* 2017; **130**: 1903–10.
- Ujjani CS, Jung SH, Pitcher B, et al. Phase 1 trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: Alliance A051103. *Blood* 2016; **128**: 2510–16.
- Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014; **32**: 3059–68.
- van der Velden VH, Cazzaniga G, Schrauder A, et al. Analysis of minimal residual disease by Ig/TCR gene rearrangements: guidelines for interpretation of real-time quantitative PCR data. *Leukemia* 2007; **21**: 604–11.
- Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. *Blood* 2008; **112**: 2687–93.
- Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. *Lancet Oncol* 2016; **17**: 48–56.
- Albertsson-Lindblad A, Freiburghaus C, Jerkeman M, Ek S. Ibrutinib in combination with anti-CD20-antibody negatively affects antibody dependent cellular cytotoxicity on mantle cell lymphoma cell lines, not reversed by the addition of lenalidomide. American Society of Hematology 59th Annual Meeting & Exposition; Atlanta, GA, USA; Dec 9–12, 2017. 1266 (abstr).
- Sagiv-Barfi I, Kohrt HE, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. *Proc Natl Acad Sci U S A* 2015; **112**: E966–72.
- Ramsay AG, Clear AJ, Fatah R, Gribben JG. Multiple inhibitory ligands induce impaired T-cell immunologic synapse function in chronic lymphocytic leukemia that can be blocked with lenalidomide: establishing a reversible immune evasion mechanism in human cancer. *Blood* 2012; **120**: 1412–21.
- Delfau-Larue MH, Klapper W, Berger F, et al. High-dose cytarabine does not overcome the adverse prognostic value of CDKN2A and TP53 deletions in mantle cell lymphoma. *Blood* 2015; **126**: 604–11.
- Pott C, Hoster E, Delfau-Larue MH, et al. Molecular remission is an independent predictor of clinical outcome in patients with mantle cell lymphoma after combined immunochemotherapy: a European MCL intergroup study. *Blood* 2010; **115**: 3215–23.